REMARKS

The Office has maintained the position that the pending claims are obvious in view of U.S. Patent No. 6,506,767 (hereafter "the '767 patent") or WO 99/01450 (which is directed to substantially the same subject matter as the '767 patent).

The Office has prefaced it reasoning in support of obviousness by stating that "enantiomeric pure or mixtures of different ratios are not 'patentable,'" and that "[e]ven optical isomers are not patentable over racemic mixtures." The logic then is that because "optical isomers are not patentable over racemic mixtures," then the presently claimed processes for preparing desloratadine polymorphic compositions are not patentable over the desloratadine polymorphic compositions disclosed in the '767 patent. Applicants assume that the Office finds support for the "per se rule" that "optical isomers are not patentable over racemic compounds" in *In re Adamson*, 275 F.2d 952 (CCPA 1960).[1] However, *In re May* shows that *Adamson* did not establish a *per se* rule, and that enantiomers can be nonobvious over racemates.[2] Indeed, the May Court held that "novel chemical compound can be nonobvious to one having ordinary skill in the art notwithstanding that it may possess a known property in common with a known structurally similar compound."[3] The reason for this finding is that an obviousness determination must consider the facts as a whole and that "properties which would have been expected must be balanced against the unexpected properties."[4] Stated another way, an obviousness analysis must balance that which is expected versus that which is unexpected.

Applicants believe that the Office has not performed this balancing test, but instead has merely asserted that Applicants' claimed processes is nothing more than routine experimentation of that which is disclosed in the '767 patent.

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[1] The Office has cited *In re Durden* 226 USPQ 359, 763 F.2d 1406 (Fed. Cir. 1985). However, Applicants believe that *In re Durden* does not support the Office's "per se rule" because the issue considered by the *Durden Court* "is whether a chemical process, otherwise obvious, is patentable because either or both the specific starting material employed and the product obtained, are novel and unobvious." *Id.* at 1408. The *Durden Court*, unlike the present matter, did not have to balance that which was expected versus that which is unexpected.

[2] *In re May*, 574 F.2d 1082 (CCPA 1978); *see also Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006).

[3] *In re May* at 1093.

[4] *Id.* at 1094.

Applicants believe that the Office appears to ignore the general teaching away expressed in the '767 patent that mixtures of desloratadine polymorphs are generally undesirable. See the '767 patent at column 1, lines 34-42 and column 4, lines 5-11. Moreover, Applicants believe that the Office has not taken into account that the '767 patent provides no reasoning, except for the specifically recited solvents, that would allow one to predict (or to expect) that a particular polymorphic composition is obtained under a particular process condition. See the '767 patent at column 4, lines 18-37. For example, the '767 patent discloses that "hexanol and methanol produced 100% polymorph form 1." See the '767 patent at column 4, lines 23-24. Based on this information alone, one might conclude that all lower alcohols would likewise produce 100% polymorph form 1. However, this is not the case because in the same sentence the '767 patent discloses that "3-methyl-1-butanol and cyclohexanol produced significant amounts of form 2." *Id.* at column 4, lines 25-26. Given this uncertainty for these particular solvents Applicants do not accept the Office's position "that polymorphs exist and screening for them via different processes is a routine experimentation for those of skill in the art." Applicants request that the Examiner reconsider the outstanding rejection by balancing the information disclosed in the '767 patent with the unexpected results that flow from the claimed processes.

Claims 1-7 and 9

Claims 1-7 and 9 are not obvious over the '767 patent because one of ordinary skill would not expect that one could obtain crystalline desloratadine Form I substantially free of Form II comprising the steps of: a) preparing a solution of desloratadine in a solvent selected from the group consisting of acetonitrile, di-methyl formamide, tetrahydrofuran and diethylcarbonate, wherein crystalline desloratadine Form I crystallizes out of the solution; and b) recovering the crystalline desloratadine Form I. One would not expect to prepare crystalline desloratadine Form I substantially free of Form II using a solvent selected from the group consisting of acetonitrile, di-methyl formamide, tetrahydrofuran and diethylcarbonate because the '767 patent does not disclose these solvents. To suggest that one would expect that such a polymorphic

composition could be obtained by the recited process, based on the '767 patent, is speculation at best. Because a determination of obviousness should not be based on mere speculation, Applicants believe that claims 1-7 and 9 are not obvious over the '767 patent.

Claims 10-12 and 15-16

Claim 10 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about 15% to about 25%, said process comprising the steps of: a) preparing a solution of desloratadine in ethyl acetate; b) combining the solution with **an anti-solvent** to precipitate the crystalline desloratadine; and c) recovering the crystalline desloratadine.

The '767 patent does not disclose or suggest preparing crystalline desloratadine using an anti-solvent. Amended claim 10 requires that the mixture of crystalline desloratadine comprises "an amount of Form II ranges from about 15% to about 25%." Applicants believe that this aspect is **unexpected** because the '767 patent discloses that crystallization of desloratadine from ethyl acetate produces "polymorph form 2 substantially free of form 1" (see the '767 patent at column 4, lines 38-40), where the term "substantially free" means "less than about 15%" (see the '767 patent at column 3, lines 60-64). How would one of ordinary skill reasonably expect that under the conditions recited in claim 10 that a mixture of crystalline desloratadine comprising an amount of Form II that ranges from about 15% to about 25% would result upon addition of an anti-solvent? Moreover, why would one of ordinary skill desire to prepare such a composition when the '767 patent provides negative comments about using polymorphic mixtures of desloratadine because doing so is "unacceptable in view of stringent GMP requirements" for use in pharmaceutical compositions? Because there is no reasonable expectation that one would obtain the recited polymorphic composition by the recited process and because the '767 patent suggests that it is undesirable to obtain such a composition, Applicants believe that claim 10, and claims dependent thereon, are unobvious over the '767 patent.

Claims 24-26

Claim 24 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about from about 2% to about 10%, said process comprising the step of: a) preparing a solution of desloratadine in a C_1 to C_4 alcohol; b) combining the solution with water to precipitate the crystalline desloratadine; and c) recovering crystalline desloratadine.

The '767 patent does not disclose or suggest preparing crystalline desloratadine using an anti-solvent, in the present claims water is the anti-solvent (see Applicants' disclosure at page 9, lines 32-33). Applicants believe that claim 24 is unexpected because the '767 patent at column 4, lines 21ff discloses "that certain alcoholic solvents, e.g., hexanol and methanol produced 100% polymorph form 1, but others, e.g., 3-methyl-1-butanol and cyclohexanol produced significant amounts of form 2." Applicants note that the '767 patent does not specifically define what the term "significant amounts" means. Since patentee has characterized "substantially free" as being the equivalent to less than about 15%, and "essentially free" as being less about 1%, then it is reasonable to assume that "significant amounts" must be equivalent to some amount greater than 16%.

Applicants note that in view of the '767 patent, some alcoholic solvents provide for pure polymorph Form I, but most alcoholic solvents provide for mixtures of both polymorphic forms that contain "significant amounts" of form II. Applicants believe that there is no suggestion contained in the '767 patent that would lead one to expect that a C_1 to C_4 alcohol would provide for a mixture of Form I and Form II in which the amount of Form II ranges from about 2% to about 10%. Couple this with the fact that the '767 patent does not disclose use of an antisolvent (*cf.* water), Applicants believe that claims 24-26 are unobvious over the '767 patent.

Claim 27

Claim 27 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine ranges from about 5% to about 6%, said process

comprising the steps of: a) preparing a solution of desloratadine in isopropanol, b) seeding the solution with Form II to increase the ratio of Form II to Form I; wherein desloratadine the mixture of crystalline desloratadine precipitates from the solution; and c) recovering the crystalline desloratadine.

The '767 patent does not disclose or suggest using isopropanol as a solvent for preparing crystalline desloratadine. Moreover, the '767 patent does not disclose or suggest "seeding the solution" so as to increase one polymorph over another. Given these two differences, Applicants believe that one of ordinary skill would not reasonably expect that one could obtain the recited polymorphic composition by the recited process. Thus, Applicants believe that claim 27 is unobvious over the '767 patent.

Claims 29 and 73 and 30

Original claim 29 is directed to a process for preparing crystalline desloratadine Form II comprising the steps of: a) melting desloratadine to obtain a molten material; b) cooling the molten material to obtain a solid; and c) grinding the solid. Claim 73, which depends on claim 29, recites that the Form II is substantially free of Form I. Original claim 30 is directed to a process for preparing a mixture of crystalline desloratadine Form I and Form II comprising the step of grinding crystalline desloratadine Form I.

Applicants note that the '767 patent does not disclose or suggest a process for preparing crystalline desloratadine by melting, cooling, and grinding. Indeed, none of these steps are disclosed in any of the references of record. Accordingly, claims 29 and 73, as well as claim 30, are unobvious over the cited references.

Claims 31-32

Claim 31 is directed to a process for preparing crystalline desloratadine Form II comprising the steps of: a) preparing a solution of desloratadine in dimethyl carbonate, wherein desloratadine Form II precipitates from the solution; and b) recovering the crystalline desloratadine Form II. Claim 32, which depends on claim 31, recites that "the Form II recovered is substantially free of Form I."

The '767 patent does not disclose or suggest preparing crystalline desloratadine using dimethyl carbonate. Indeed, the '767 patent discloses at column 4, lines 21-22, that "we tried many solvent systems, most of which produced only mixtures of polymorphs." However, some solvents, such as methanol and hexanol "produced 100% polymorph form 1." Again, Applicants ask the Examiner to explain how one of ordinary skill would expect a result based on the disclosure of the '767 patent when dimethyl carbonate is not utilized as a solvent? Because the '767 patent provides no basis for prediction, other than speculation, Applicants believe that claims 31-32 are unobvious in view of the '767 patent.

Claim 33

Claim 33 is directed to a process for preparing a mixture of crystalline desloratadine composition comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about 15% to about 25%, said process comprising the steps of: a) preparing a solution of desloratadine in i-butyl acetate, wherein Form I precipitates from the solution; and b) recovering the precipitate.

The '767 patent does not disclose or suggest using i-butyl acetate to prepare crystalline desloratadine. The '767 patent discloses ethyl acetate, but ethyl acetate is not suggestive of i-butyl acetate. Even if the Examiner considered ethyl acetate to be suggestive of i-butyl acetate, the Examiner would also have to consider that ethyl acetate produces "crystalline polymorph form 2 substantially free of form 1" (see the '767 patent at column 4, lines 38-40). Compositionally speaking, the composition amount recited by claim 33 is the diametric opposite of what is disclosed by the '767 patent. Accordingly, Applicants believe that this aspect is unexpected in view of the disclosure of the '767 patent so that this claim is unobvious over the same.

Claims 35-36

Claim 35 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about 2% to about 6%, said process

comprising the steps of: a) preparing a solution of desloratadine in a solvent selected from the group consisting of isopropanol and i-butanol, wherein desloratadine Form I precipitates from the solution; and b) recovering the crystalline desloratadine.

The '767 patent does not disclose or suggest preparing crystalline desloratadine using a solvent containing either isopropanol or i-butanol. Because one cannot expect a certain result, without speculation, in the absence of data to guide the way, Applicants believe that claims 25-36 are unobvious over the '767 patent.

Claims 38-40

Original claim 38 is directed to process for preparing a mixture of crystalline Form I and Form II of desloratadine comprising the step of drying desloratadine Form I crystals obtained by crystallization from a C_1 to a C_4 alcohol.

Applicants note that the '767 patent does not disclose or suggest that a mixture of crystalline Form I and Form II of desloratadine comprising the step of drying desloratadine Form I crystals obtained by crystallization from a C_1 to a C_4 alcohol.

Accordingly, claim 38 is unobvious over the references of record.

Claims 41-45

Original claim 41 is directed to a process for making a mixture of crystalline desloratadine Form I and Form II comprising the steps of combining a solution of desloratadine in a suitable solvent with an anti-solvent containing seeds of both Form I and Form II of desloratadine to precipitate the mixture, and recovering the mixture.

As noted above, the '767 patent does not disclose a process for preparing desloratadine by combining a solution of desloratadine in a suitable solvent with an anti-solvent, especially an anti-solvent containing seeds of both Form I and Form II.

Accordingly, rejection of these claims is improper.

Claims 46-49

Claim 46 is directed to a process for preparing a mixture of desloratadine crystalline comprising at least about 25% of both Form I and Form II, said process

comprising the steps of: a) preparing a solution of desloratadine in a solvent selected from the group consisting of ethyl acetate and iso-butyl acetate, in a mixture with about 3% to about 20% C_1 to C_4 alcohol by volume, wherein the mixture of Form I and II precipitates from the solution; and b) recovering the mixture.

The '767 patent does not disclose or suggest preparing crystalline desloratadine using either ethyl acetate or iso-butyl acetate in combination with about 3% to about 20% C_1 to C_4 alcohol by volume. Indeed, the '767 patent does not disclose or suggest obtaining crystalline desloratadine using any solvent mixtures.

Accordingly, rejection of these claims is improper.

Claims 50-54

Claim 50 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, said process comprising the steps of: a) preparing a solution of desloratadine in iso-butyl acetate; b) combining the solution with a C_6 to C_{12} aromatic hydrocarbon to precipitate the mixture, wherein the combining may be carried out before, after or during crystallization; and c) recovering the mixture.

As noted in the comments in the previous sub-section, the '767 patent does not disclose or suggest preparing crystalline desloratadine using iso-butyl acetate. Furthermore, the '767 patent does not disclose adding an anti-solvent, such as a C_6 to C_{12} aromatic hydrocarbon in order to precipitate the mixture.

Accordingly, rejection of these claims is improper.

Claim 55-56

Claim 55 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, said process comprising the steps of: a) preparing a solution of desloratadine in iso-butyl acetate; b) combining the solution with iso-butyl acetate at a temperature lower than the solution to crystallize the mixture; and c) recovering the mixture.

The '767 patent does not disclose preparing crystalline desloratadine using iso-butyl acetate at all. Moreover, the '767 patent provides no hint to mix an iso-butyl acetate

solution containing desloratadine with iso-butyl acetate at a lower temperate than the solution.

Accordingly, rejection of these claims is improper.

Claims 57-59

Claim 57 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, said process comprising the steps of: a) preparing a solution of desloratadine in ethyl acetate; b) seeding the solution with a mixture of Form I and Form II; c) combining the solution with a C_5 to C_{12} saturated hydrocarbon, wherein the combining may be carried out before, after or during crystallization; and d) recovering the mixture of desloratadine Form I and II.

The '767 patent does disclose preparing crystalline desloratadine using ethyl acetate alone. However, the '767 patent does not disclose or suggest seeding the solution with a mixture of Form I and Form II and combining the solution with a C_5 to C_{12} saturated hydrocarbon. These additional aspects are not at all disclosed or suggested.

Accordingly, rejection of these claims is improper.

Claims 60-65

Claim 60 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, said process comprising the steps of: a) preparing a solution of desloratadine in 2-propanol and toluene, wherein the mixture of Forms I and II precipitates from the solution; and b) recovering the mixture.

The '767 patent does note disclose or suggest preparing crystalline desloratadine using a mixture of any solvent, especially that recited in claim 60.

Accordingly, rejection of these claims is improper.

Claims 66-67

Claim 66 is directed to a process for preparing a mixture of desloratadine comprising Form I and Form II, said process comprising the steps of: a) providing a first solution of desloratadine in toluene; b) evaporating the toluene to obtain a residue; c)

dissolving the residue in a mixture of toluene and a C_1 to C_4 alcohol to obtain a second solution; d) cooling the second solution to obtain a slurry; e) combining the slurry with a C_5 to C_{12} saturated hydrocarbon to precipitate the mixture; and f) recovering the mixture.

The '767 patent does not disclose or suggest using toluene at all (see Tables 1-2 in Response filed May 3, 2007). This being the case, how can the disclosure of the '767 patent, in view of any extraneous comments, further suggest dissolving the residue in a mixture of toluene and a C_1 to C_4 alcohol to obtain a second solution; cooling the second solution to obtain a slurry; combining the slurry with a C_5 to C_{12} saturated hydrocarbon to precipitate the mixture; and recovering the mixture. Because none of these aspects are disclosed or suggested, the claimed process is unobvious over the references of record.

Accordingly, rejection of these claims should be withdrawn.

Claims 68-71

Claim 68 is directed to a process for preparing a mixture of desloratadine comprising Form I and Form II, said process comprising the steps of: a) combining desloratadine acetate, toluene and KOH to obtain a reaction mixture; b) heating the mixture, whereby two phases are obtained; c) separating the phases; d) concentrating the separated organic phase; e) dissolving the obtained concentrate in a toluene-2-propanol mixture containing less than about 20% 2-propanol by volume; f) cooling the solution to obtain a slurry; g) combining the slurry with cold n-heptane; and h) recovering mixture of desloratadine forms I and II.

The '767 patent does not disclose or suggest using toluene at all (see Tables 1-2 in Response filed May 3, 2007). Like claims 66-67 noted above, there can be no further suggestion of additional process steps.

Accordingly, rejection of these claims should be withdrawn.

Claim 72

Original claim 72 is directed to process for preparing crystalline desloratadine Form II comprising the steps of crystallizing desloratadine from toluene, and recovering the crystalline form.

The '767 patent does not disclose or suggest using toluene at all (see Tables 1-2 in Response filed May 3, 2007).

Accordingly, rejection of this claim should be withdrawn.

Claims 74-79

Claim 74 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about 35% to about 40%, said process comprising the steps of: a) preparing a solution of desloratadine in chloroform; b) combining the solution with an anti-solvent to precipitate desloratadine Form I; and c) recovering the mixture of crystalline desloratadine.

The '767 patent discloses that "[c]hlorinated solvents…produced form 1 substantially free of form 2 but the compounds were discolored" (see the '767 patent at column 4, lines 25-26). The process recited in new claim 74 provides for a desloratadine mixture that is not substantially free of Form II. Instead, the amount of Form II, based on the total amount of desloratadine, ranges from about 35% to about 40%. This is outside the range that is predicted based on the disclosure of the '767 patent. Couple this with the fact that the '767 patent does not disclose a crystallization process that requires combination of a desloratadine solution with an anti-solvent, Claims 74-79 are unobvious over the references of record.

Accordingly, rejection of this claim should be withdrawn.

Claims 80-87

Claim 80 is directed to a process for preparing a mixture of crystalline desloratadine comprising Form I and Form II, wherein the amount of Form II, based on the total amount of desloratadine, ranges from about 2% to about 6%, said process comprising the steps of: a) preparing a solution of desloratadine in chloroform; b) combining the solution with an anti-solvent to precipitate desloratadine Form I; and c) recovering the mixture of crystalline desloratadine.

The '767 patent does not disclose a crystallization process that requires combination of a desloratadine solution with an anti-solvent.

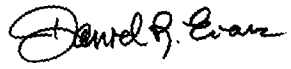
Accordingly, claims 80-87 are unobvious over the references of record.

In view of the amendments to the claims and the comments provided herein, Applicants believe that the present application is in a condition for allowance. Acknowledgement of the same is respectfully requested.

Applicants concurrently filed with the present response a Request for a Three-Month Extension of Time under 37 CFR 1.136(a) with an authorization to charge any requisite fee to Applicants' representative Deposit Account 13-2725. If for any reason the Request for Extension of Time is separated from the present response, then Applicants authorize the Office to charge the above-noted Deposit Account to pay any necessary fees so as to maintain the pendency of the present application.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(404) 954-5061



Daniel R. Evans, Ph.D.
Registration No. 55,868

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